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Frailty Prevalence, Incidence, and Association with Incident Disability in the Italian Longitudinal Study on Aging

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Keywords
Frailty · Disability · Cohort study · Aging · Epidemiology

Abstract

Introduction: Data on frailty frequency are heterogeneous and mostly based on cross-sectional studies. Little is known about frailty development and progression over time. Our aim was to conduct a systematic analysis of frailty prevalence and incidence in a large cohort of older adults and to evaluate the association with incident disability, in order to tackle the current paucity and fragmentation of longitudinal data on frailty. ***Methods:*** As secondary analysis of the Italian Longitudinal Study on Aging (ILSA) population-based cohort (n = 5,632, 65–84), frailty status was operationalized according to Fried criteria (n = 2,457). Weighted prevalence and incidence rates were calculated at each ILSA wave (T0 1992–1993, T1 1995–1996, T2 2000–2001). The association with incident disability in Activities of Daily Living (ADL) or Instrumental Activities of Daily Living (IADL) was investigated through Cox proportional hazard models, controlling for possible confounders. ***Results:*** Prevalence of frailty and pre-frailty at baseline (mean age 71.6 years; women 58.9%) were 4.0% (95% confidence interval [CI]: 3.4–4.6) and 44.6% (95% CI: 43.1–46.1), respectively. Incidence rates per 1,000 person-years for the T0–T1 interval were 7.3 (95% CI: 5.2–9.3) for frailty and 83.7 (95% CI: 73.6–93.8) for pre-frailty. Prevalence and incidence of frailty, and to a lesser degree of pre-frailty, were overall higher for women and increased with age, yet no increasing trend with advancing age was detected for pre-frailty incidence. Frailty incidence rates were significantly higher among pre-frail than non-frail individuals at follow-up entry. After full adjustment, being frail markedly increased the risk of incident disability in ADL (hazard ratio [HR] 3.58, 95% CI: 1.97–6.52) and IADL (HR 2.56, 95% CI: 1.58–4.16) over a 4-year period. ***Discussion/Conclusion:*** According to our findings, frailty is common among older people and is a strong and independent predictor of disability. Further research on factors and characteristics related to frailty progression, and especially remission, over time is crucial to calibrate effective public health preventive measures.

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Introduction

Frailty is a progressive, age-related, functional decline, which confers extreme vulnerability to endogenous and exogenous stressors, leading to increasing risk of adverse health outcomes [1]. Although a common definition and assessment instrument for research and clinical practice is yet to be achieved [2], the conceptual and theoretical basis of frailty, as a complex, multifaceted, dynamic process, is well established [3, 4]. It has been clarified that frailty condition involves physical, psychological, and socio-economic aspects, and that it should be seen in a lifelong perspective but not as an inevitable consequence of the aging process [5]. Though often interchangeably used as synonymous, frailty is a distinct entity from either multimorbidity or disability; the first is a risk factor for frailty, and the latter is one of its major outcomes, together with hospitalization and mortality [6, 7].

Frailty is gradually gaining wider recognition as one of the major challenges of global population aging and a significant public health concern [8, 9]. Being a dynamic condition with a fluctuating course, where transitions between frailty states are frequent [10, 11] and recovery is possible [12], frailty offers ample potential for prevention and management through public health and clinical interventions [5]. Understanding the real burden of frailty, its frequency, and progression in the population is essential to calibrate an adequate public health response, balancing available resources against individual and collective needs, with large benefits for individuals, their families, and society as a whole and a considerable reduction in public health expenditures.

Current epidemiological evidence on frailty is mostly based on cross-sectional studies. It shows that frailty is common among older people, approximately affecting about 10% of community-dwelling population over 65 years of age, with a reported prevalence varying enormously according to the adopted classification of frailty, the study setting, and the specific characteristics of participants [13, 14]. On the other hand, despite its dynamic nature, there is a remarkable paucity of longitudinal data about how frailty develops and progresses over time. Studies on frailty incidence are sporadic, extremely heterogeneous, and almost exclusively based on incidence proportions rather than person-time rates, thus further limiting comparability of results because of the heavy influence of follow-up length on the cumulative incidence measure [15, 16]. The objective of the present study was to calculate prevalence and incidence of frailty in a large cohort of older Italians (aged 65–84 years), followed up over three longitudinal waves, and to evaluate the predictive role of frailty on incident disability, in order to tackle the current fragmentation of data on the frequency of frailty at the population level, setting the basis for an in depth and systematic analysis of its progression over time.

Materials and Methods

Study Design and Sample

This was a secondary analysis of data deriving from the Italian Longitudinal Study on Aging (ILSA), an extensive epidemiological study aimed at investigating frequency, risk, and protective factors of major age-associated conditions and of physical and functional changes in an Italian community-based cohort [17]. A random sample of 5,632 subjects aged 65–84 years, both community-dwelling and institutionalized, stratified by age and sex using an equal allocation strategy, was selected from the population registries of eight municipalities located across Italy. Ethical approval and informed consent from participants were obtained before starting the study.

The ILSA cohort was first examined in 1992–1993 (T0) and extensively re-examined in two longitudinal waves carried out in 1995–1996 (T1) and 2000–2001 (T2). The three surveys had a two-phase design. In phase 1 (screening), all participants underwent: (a) a personal interview on sociodemographic characteristics, family and medical history, self-reported health problems, and risk factors; (b) a nurse visit, including a fasting blood sample; and (c) a physical examination by a physician, including a general clinical and functional assessment, a neurological examination, a neuropsychological battery, and diagnostic tests, such as spirometry, electrocardiography, and retinal photography. In phase 2 (clinical confirmation), participants who screened positive for chronic conditions under study were examined by a specialist to confirm or exclude suspected diagnoses according to standardized criteria, based on clinical examination and the review of medical records [18]. Detailed data on vital status and cause-specific mortality have been periodically retrieved from municipalities and through record-linkage with the national mortality register (still ongoing follow-up).

As shown in Figure 1, 170 out of the original selected sample were ineligible for inclusion in the study because of being dead or having moved before the study start. Of the remaining 5,462 eligible subjects, 941 refused to participate or could not be contacted. Participants in the present analysis were the 2,239 individuals with adequate information to retrospectively assess frailty from at least one ILSA survey (T0 n = 1,992; T1 n = 1,279; T2 n = 1,094; unweighted data). Less than 2% of them were in hospital (1.1%) or nursing home (0.6%) at baseline.

Frailty

Frailty was defined according to the physical phenotype criteria elaborated by Fried and colleagues [19]. The five frailty domains were operationalized as follows:

1. *Weight loss*, self-reported unintentional (independent from diet or exercise) weight loss >5 kg in the last year.
2. *Exhaustion*, negative answer to question 21 – "Do you feel full of energy?" – of the 30-item version of the Geriatric Depression Scale (GDS-30) [20] and overall GDS score ≥10.

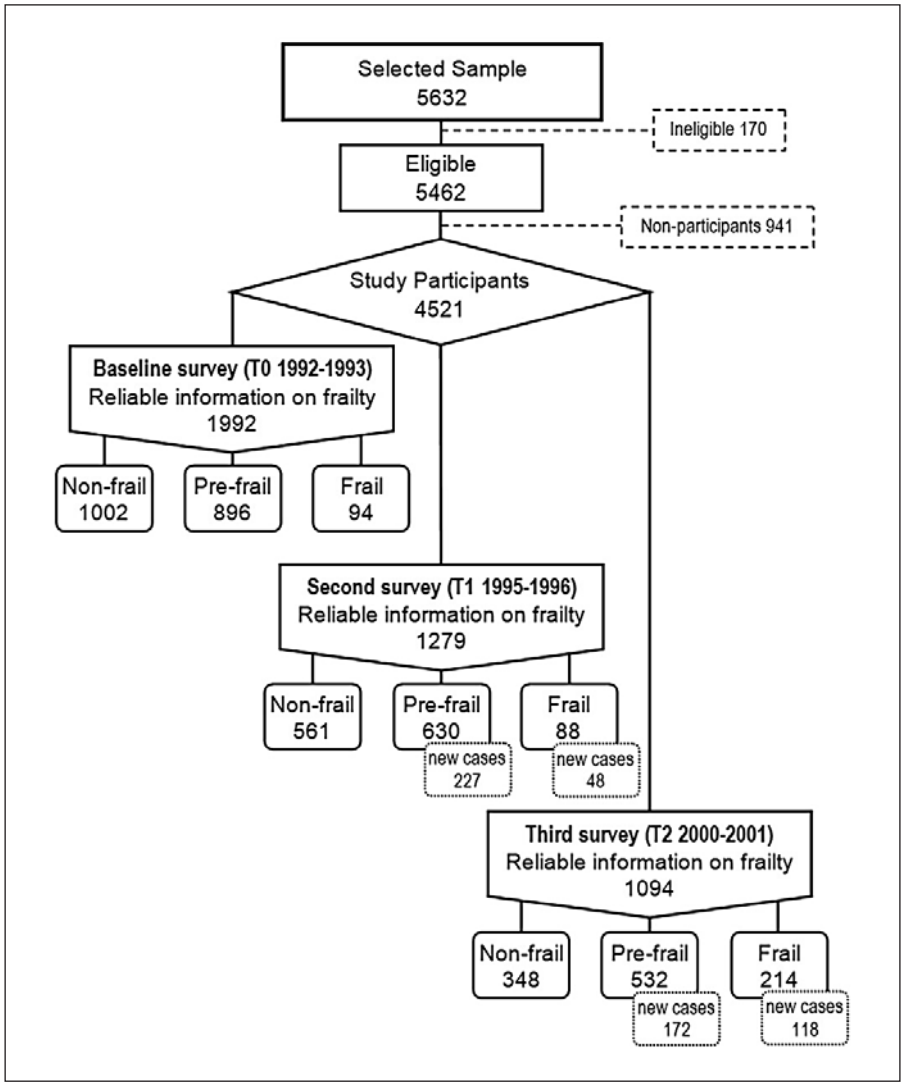

Fig. 1. Attrition of the ILSA population in each step of the frailty study (unweighted data, number).

3. *Weakness*, inability to perform the chair-stand test without help or using arms [21].
4. *Slowness*, mean time ≥7 s at the 5-m gait speed test [21].
5. *Low physical activity*, current sedentary or low physical activity derived from (a) T2 detailed retrospective assessment of physical activity by age intervals and during the previous year or (b) in case of missing information in T2, Activities of Daily Living (ADL) scale [22] item 4 > 1 (able to get in and out of bed only with aids or bedridden) and some degree of dependence in ≥3 of the following everyday tasks: shopping, preparing meals, doing housework, driving, or using public means of transports, as assessed by specific items of the Instrumental Activities of Daily Living (IADL) scale [23].

Only subjects with reliable information on all five criteria were included in the present analysis. They were categorized as frail if three or more criteria out of five were met, pre-frail in case of presence of one or two of them, and non-frail if none was fulfilled (0 = non-frail; 1–2 = pre-frail; ≥3 = frail).

Disability

The degree of dependence in the main basic activities of daily living – hygiene, dressing, toileting, locomotion, continence, eating – was assessed in all ILSA surveys through the ADL scale [22] and categorized as dependent in ≥1 ADL or independent in all. The level of disability in more sophisticated tasks of everyday life – using telephone, shopping, preparing meals, doing housework and laundry, driving or using public transport, handling medications, and managing money – was assessed through the IADL scale [23]. Participants were classified as dependent in ≥1 IADL or independent in all applicable IADL. The outcome presented in this work in relation to frailty status at baseline is the occurrence of incident disability in ADL and IADL at second and third ILSA surveys, among subjects free of ADL or IADL disability at baseline.

Covariates

Covariates were selected from baseline data among factors frequently reported as associated with frailty. The sociodemographic and health characteristics included in the analysis were: sex; age;

education (years of schooling 0–3, 4–7, ≥8); marital status (married or living with a partner vs. non-married); cohabitation status (living alone vs. living with someone); smoking status (current smoker, ex-smoker, never smoker); alcohol consumption (current drinker, ex-drinker, never drinker); body mass index (BMI, kg/m^2) categorized into underweight <18.5, normal weight 18.5–24.9, overweight 25–29.9, obesity ≥30; cognitive impairment according to the Mini-Mental State Examination (MMSE) score [24] (mild/severe if the MMSE score <24 vs. absent ≥24); depressive symptoms as assessed through GDS-30 [20] (mild/severe if GDS score ≥10 vs. absent <10); clinical diagnosis of hypertension, myocardial infarction, angina pectoris, cardiac arrhythmia, congestive heart failure, diabetes, peripheral artery disease, stroke, dementia, parkinsonism, and distal symmetric neuropathy [17]; comorbidity (2 or more of the previous pathologic conditions).

Statistical Analysis

To generalize the ILSA sample to the Italian population, a set of weights was defined and applied to all analyses according to the sample fraction and the age and sex distribution of the Italian reference population according to the 1991 census data. Main characteristics at baseline were summarized through mean and standard deviation (SD) for continuous variables and counts and percentages for categorical variables. For continuous variables, normal distributions were tested using the Kolmogorov-Smirnov test. Descriptive statistics, using the χ^2 or exact test for categorical variables and the Student t-test for the continuous ones, were applied to compare the distribution of baseline characteristics between subjects with and without complete frailty information (participants vs. non-participants) and according to frailty status at baseline.

Prevalence and 95% confidence interval (CI) of frailty status (frail, pre-frail, and non-frail) were calculated at different time points (T0, T1, and T2) and stratified by sex and 5-year age classes. The percentage contribution of each of the five domains to the fulfillment of frailty and pre-frailty criteria was also measured.

The incidence of pre-frailty and frailty was estimated for two follow-up segments, one going from the first to the second survey (T0–T1) and the other covering the overall period of observation (T0–T2), with a mean follow-up duration of 4 and 9 years, respectively. The intermediate interval T1–T2 was not analyzed for a better comparison of obtained results and to avoid the selective survival bias. To calculate incident frailty, both non-frail and pre-frail subjects at baseline (T0) were considered at risk and included in the denominator, while for incident pre-frailty, only non-frail individuals were selected. The incidence was estimated as incidence proportion (percentage of new cases on the population at risk) and of incidence rates per 1,000 person-years (number of new cases divided by the total time each person in the population was at risk of developing the condition) stratified by age and sex; age bands were based on age at the baseline assessment. The contribution in person-years of non-incident cases to the denominator was calculated as the time between the first and the follow-up examination or death. The mid-point of the interval was used to calculate person-years for incident cases of frailty/pre-frailty or for persons lost to follow-up, given the impossibility to establish the date of onset or withdrawal.

The association between frailty status at baseline and incident disability in ADL or IADL observed from the first survey to the second and third assessments (T0–T1; T0–T2) was evaluated through Cox proportional hazard models, adjusting at first for age and sex and then also for other covariates significantly related to frailty at preliminary descriptive analysis. The proportional hazard assumption was verified considering Schoenfeld's residuals of the covariates. Adjusted hazard ratios (HRs) and 95% CI were calculated.

All tests were two-sided with a significance level of $p < 0.05$. The analyses were performed using SAS statistical package, release 9.4 (SAS, Cary, NC, USA). Procedures for complex surveys (SURVEYMEANS, SURVEYREG, SURVEYFREQ, SURVEYPHREG, and SURVEYLOGISTIC), considering the ILSA sampling strategy, were applied.

Results

The final weighted sample with complete information on frailty in at least one of the ILSA surveys amounted to 2,457 subjects: 2,178 individuals at baseline (T0, women 58.9%; mean age ± SD 71.6 ± 5.1 years), 1,440 at second survey (T1, women 56.2%; 74.5 ± 4.9 years), and 1,261 at third survey (T2, women 54.6%; 78.9 ± 4.7 years). Comparing participants included in the analysis with those excluded because of incomplete information to assess frailty status (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000525581), the latter were older; more likely to be male; less frequently married; with lower levels of education, alcohol consumption, and BMI; more frequently affected by cognitive impairment and depressive symptoms; with significantly higher dependence in ADL and IADL; and generally in worst health conditions.

Prevalence

The overall weighted prevalence of frailty was 4.0% (95% CI: 3.4–4.6) at baseline, 6.2% (95% CI: 5.3–7.1) at T1, and 18.0% (95% CI: 16.5–19.5) at T2. The corresponding prevalence of pre-frailty at each time point was 44.6% (95% CI: 43.1–46.1), 49.9% (95% CI: 48.0–51.7), and 48.8% (95% CI: 46.8–50.8), respectively (Table 1). As shown in Figure 2, prevalence rates observed in the three ILSA examinations were significantly higher for women, with a frequency of frailty about twice that of men, and increased steeply with advancing age.

The distribution of sociodemographic and health characteristics by frailty status at the first survey (Table 2) showed that pre-frail and frail subjects were older (72.3 ± 5.2 years and 75.8 ± 5.0 years, respectively, vs. 70.7 ± 4.7 non-frail) and more likely to be female (70.3% and 78.2%, respectively, vs. 47.4% non-frail). They also were less educated and less frequently married than non-frail participants; the higher proportion of living alone subjects was in the pre-frail group. In comparison with non-frail participants, pre-frail and frail older adults were more likely

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Table 1. Prevalence of frailty status in the ILSA cohort at the three surveys (T0 *n* = 2,178, T1 *n* = 1,440, T2 *n* = 1,261) by sex and age (weighted data)

	Non-frail			Pre-frail			Frail		
	T0	T1	T2	T0	T1	T2	T0	T1	T2
Overall									
Number	1,120	633	419	971	718	615	87	89	227
% (95% CI)	51.4 (50.0–52.9)	44.0 (42.1–45.8)	33.2 (31.4–35.1)	44.6 (43.1–46.1)	49.9 (48.0–51.7)	48.8 (46.8–50.8)	4.0 (3.4–4.6)	6.2 (5.3–7.1)	18.0 (16.5–19.5)
Sex, number									
Women	531	272	163	683	474	370	68	63	155
Men	589	361	256	288	244	245	19	26	72
Sex, % (95% CI)									
Women	41.4 (39.4–43.4)	33.6 (31.2–36.1)	23.7 (21.3–26.1)	53.3 (51.2–55.3)	58.6 (56.0–61.2)	53.8 (51.0–56.7)	5.3 (4.3–6.3)	7.8 (6.4–9.1)	22.5 (21.2–24.8)
Men	65.7 (63.6-67-8)	57.2 (54.5–59.9)	44.7 (41.9–47.5)	32.1 (30.1–34.3)	38.7 (36.0–41.3)	42.8 (39.9–45.6)	2.1 (1.5–2.7)	4.1 (3.1–5.2)	12.6 (10.8–14.4)
Age, number									
65–69	546	81	–	336	67	–	10	5	–
70–74	359	331	72	319	335	65	26	30	18
75–79	153	142	257	207	184	319	26	20	91
80+	62	79	90	109	132	231	25	34	118
Age, % (95% CI)									
65–69	61.2 (58.8–63.6)	52.9 (46.7–59.4)	–	37.7 (35.3–40.1)	43.8 (37.6–50.3)	–	1.1 (0.5–1.6)	3.3 (0.9–5.1)	–
70–74	51.0 (48.3–53.5)	47.6 (44.8–50.2)	46.5 (40.4–52.5)	45.3 (42.7–48.0)	48.1 (45.4–50.9)	41.9 (35.9–48.0)	3.7 (2.7–4.8)	4.3 (3.2–5.4)	11.6 (7.7–15.5)
75–79	39.6 (36.5–43.1)	41.0 (37.4–44.7)	38.5 (35.8–41.2)	53.6 (50.1–57.0)	53.2 (49.4–56.8)	47.8 (45.1–50.7)	6.7 (4.8–8.5)	5.8 (4.0–7.7)	13.6 (11.7–15.5)
≥80	31.6 (27.5–36.2)	32.2 (28.4–36.4)	20.5 (17.8–23.1)	55.6 (50.5–60.0)	53.9 (49.4–58.2)	52.6 (49.2–55.9)	12.8 (9.5–16.3)	13.9 (10.8–16.7)	26.9 (24.0–29.9)

ILSA, Italian Longitudinal Study on Aging; T0, Italian Longitudinal Study on Aging first survey carried out in 1992–1993; T1, Italian Longitudinal Study on Aging second survey 1995–1996; T2, Italian Longitudinal Study on Aging third survey 2000–2001; CI, confidence interval.

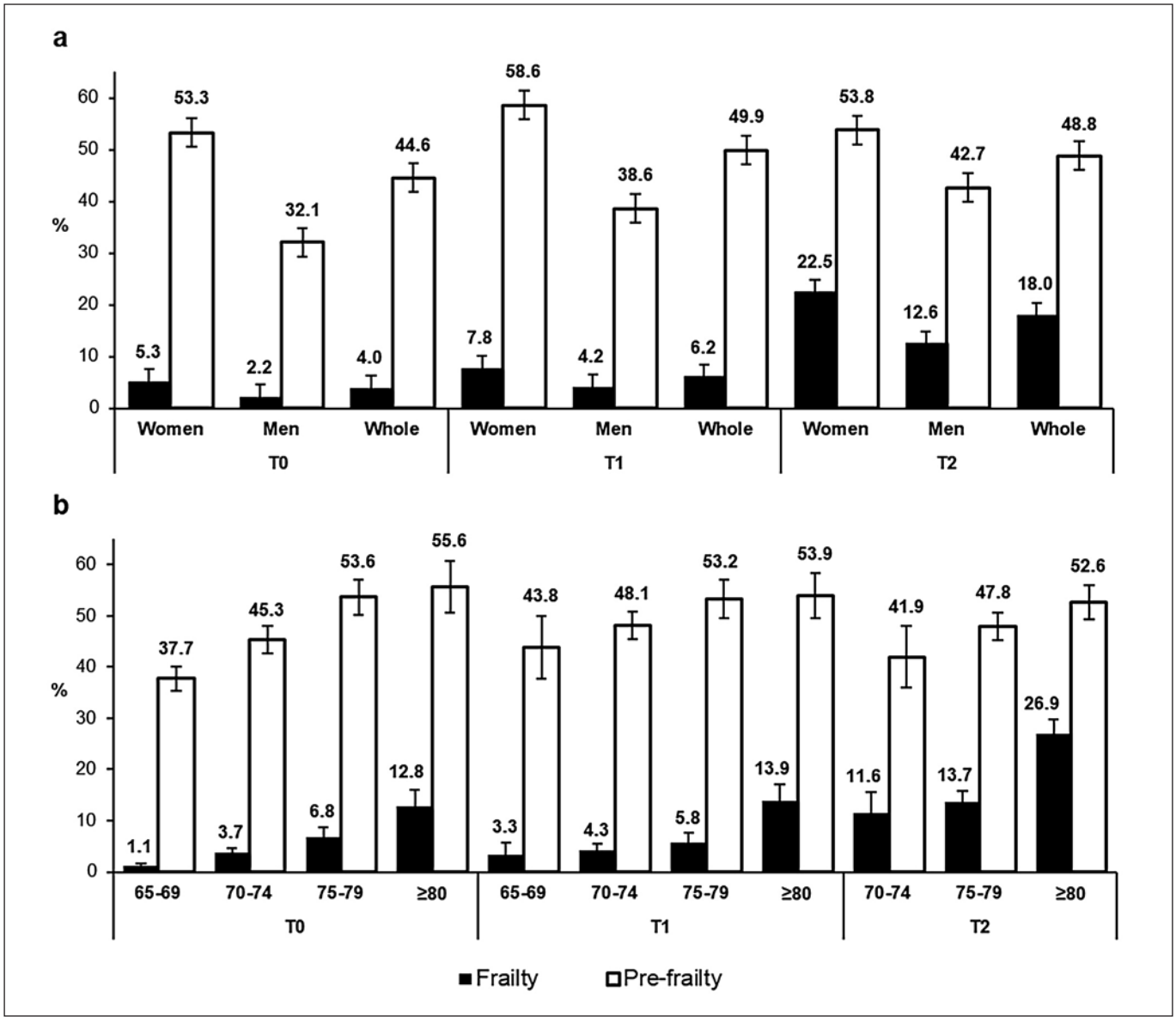

Fig. 2. Prevalence of frailty and pre-frailty in the ILSA cohort at different time points (T0 n = 2,178, T1 n = 1,440, T2 n = 1,261) by sex (**a**) and age class (**b**) (weighted data). T0, Italian Longitudinal Study on Aging first survey carried out in 1992–1993; T1, Italian Longitudinal Study on Aging second survey 1995–1996; T2, Italian Longitudinal Study on Aging third survey 2000–2001.

to be in the extreme categories of BMI classes (i.e., underweight and obesity) and had a lower proportion of current smokers or alcohol drinkers, probably also attributable to the so-called sick-quitter effect. Frail participants, and to a lesser degree the pre-frail group, had a significantly higher prevalence of cognitive impairment and depressive symptoms (about four times for frail than non-frail, $p < 0.0001$), of comorbidity (almost double for frail individuals, $p < 0.0001$), and of most of the investigated health conditions, with the exception of hypertension and arteriopathy that showed no significant difference in the distribution by frailty status.

In all assessments and almost independently from sex, the criterion that most contributed to the Fried phenotype definition was low gait speed, met in almost 100% of frail participants and around 70% of pre-frail. The least prevalent criterion was weakness for pre-frailty and weight loss for frailty definition (online suppl. Table 2).

Table 2. Baseline characteristics by frailty status at first ILSA survey (T0) (weighted data)

Variables[a]	T0 1992–1993				
	whole[b]	non-frail[c]	pre-frail[d]	frail[e]	*p* value
Sex, females	1,282 (58.9)	531 (47.4)	683 (70.3)	68 (78.2)	<0.0001
Age, years	71.6±5.1	70.7±4.7	72.3±5.2	75.8±5.0	<0.0001
Years of schooling, *n* (%)					
0–3	562 (26.7)	252 (23.4)	274 (29.1)	36 (42.2)	
4–7	905 (43.1)	492 (45.7)	385 (41.0)	28 (33.1)	0.0005
≥8	635 (30.2)	333 (30.9)	281 (29.9)	21 (24.7)	
Marital status, married	1,378 (63.2)	784 (70.0)	545 (56.1)	49 (56.3)	<0.0001
Cohabitation status, living alone	409 (18.8)	188 (16.8)	208 (21.4)	13 (15.1)	0.0189
Alcohol consumption					
Current drinker	1,531 (70.3)	812 (72.5)	669 (68.9)	50 (57.5)	
Ex-drinker	282 (12.9)	137 (12.2)	127 (13.1)	18 (20.7)	0.0213
Never drinker	365 (16.8)	172 (15.3)	174 (17.9)	19 (21.8)	
Smoking status					
Current smoker	369 (17.0)	223 (19.9)	141 (14.5)	5 (5.7)	
Ex-smoker	632 (29.0)	379 (33.8)	235 (24.2)	18 (20.7)	<0.0001
Never smoker	1,177 (54.0)	518 (46.3)	595 (61.3)	64 (73.6)	
BMI, kg/m^2					
Underweight (<18.5)	21 (1.0)	6 (0.5)	12 (1.3)	3 (3.7)	
Normal weight (18.5–24.9)	645 (30.1)	344 (31.1)	276 (28.9)	25 (30.5)	0.0373
Overweight (25–29.9)	997 (46.5)	529 (47.8)	434 (45.4)	34 (41.5)	
Obese (≥30)	481 (22.4)	228 (20.6)	233 (24.4)	20 (24.3)	
Cognitive impairment, MMSE <24	183 (8.4)	67 (6.0)	95(9.8)	21(23.7)	<0.0001
Depressive symptoms, GDS ≥10	747 (34.9)	252 (22.3)	423 (44.4)	72 (83.7)	<0.0001
Angina	158 (7.3)	67 (6.0)	80 (8.2)	11 (13.1)	0.0120
Myocardial Infarction	143(6.6)	60 (5.3)	74 (7.7)	9 (10.4)	0.0220
Heart Failure	88 (4.1)	23 (2.1)	50 (5.2)	15 (16.8)	<0.0001
Arrhythmia	509 (23.6)	248 (22.6)	233 (24.1)	28 (32.8)	0.0702
Hypertension	1,394 (72.1)	708 (71.8)	627 (72.3)	59 (73.6)	0.9303
Diabetes	256 (11.8)	114 (10.2)	128 (13.3)	14 (16.1)	0.0421
Dementia	24 (1.1)	3 (0.3)	11 (1.1)	10 (12.1)	<0.0001
Parkinsonism	30 (1.4)	9 (0.8)	15 (1.6)	6 (8.3)	<0.0001
Stroke	85 (4.5)	32 (3.4)	39 (4.6)	14 (19.8)	<0.0001
Neuropathy	122 (5.8)	52 (4.7)	59 (6.4)	11 (14.8)	0.0008
Arteriopathy	98 (5.4)	42 (4.4)	51 (6.3)	5 (7.5)	0.1205
Comorbidity, ≥2 diseases	791 (36.3)	357 (31.9)	382 (39.3)	52 (60.4)	<0.0001

BMI, body mass index; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale. [a] Data are expressed as mean ± SD for continuous variables and as *n* (%) for categorical variables; percentages may not total 100 because of rounding or missing information in some categories. [b] *n* = 2,178. [c] *n* = 1,120. [d] *n* = 971. [e] *n* = 87.

Incidence

The population at risk of frailty (robust or pre-frail at baseline) for the first follow-up segment (T0–T1) and for the overall period of observation (T0–T2) included 2,091 subjects (mean age ± SD 71.4 ± 5.0 years; 58.1% women), while the population at risk of pre-frailty (robust at entry) was composed of 1,120 participants (mean age ± SD 70.7 ± 4.7 years; 47.4% women). New cases of frailty observed during the follow-up segment T0–T1 were 2.3% (women 2.6% vs. men 1.8%) of the population at risk and 7.7% (women 9.1% vs. men 5.8%) for the period T0–T2. The corresponding incidence proportions of pre-frailty were 23.6% (women 28.2% vs. men 19.4%) for the T0–T1 interval and 24.1% (women 25.4% vs. men 22.9%) for the overall follow-up period T0–T2.

Table 3 shows the number of new cases and the age- and sex-specific incidence rates of pre-frailty and frailty for the two follow-up segments under investigation. Weighted incidence rates of frailty and pre-frailty per 1,000 person-years were, respectively: 7.3 (95% CI: 5.2–9.3) and 83.7

Table 3. Incidence rates per 1,000 person-years of pre-frailty and frailty in the ILSA cohort at different follow-up intervals, by sex and age (weighted data)

	Pre-frailty			Frailty		
	new cases, *n*	person-years at risk	incidence rate[a] (95% CI)	new cases, *n*	person-years at risk	incidence rate[a] (95% CI)
T0–T1						
Overall	264	3,155.3	83.7 (73.6–93.8)	48	6,568.0	7.3 (5.2–9.3)
Sex			*			
Women	150	1,415.3	106.0 (89.0–123.0)	32	3,723.5	8.6 (5.6–11.6)
Men	114	1,740.0	65.5 (53.5–77.5)	16	2,844.5	5.6 (2.9–8.4)
Age at T0						*
65–69	134	1,560.2	85.9 (71.4–100.4)	15	2,848.8	5.3 (2.6–7.9)
70–74	85	1,015.3	83.7 (65.9–101.5)	13	2,185.1	6.0 (2.7–9.2)
75–79	32	425.7	75.2 (49.1–101.2)	11	1,049.1	10.5 (4.3–16.7)
≥80	13	154.1	84.4 (38.5–130.2)	9	485.0	18.6 (6.4–30.7)
T0–T2						
Overall	270	6,800.8	39.7 (35.0–44.4)	161	13,798.8	11.7 (9.9–13.5)
Sex						*
Women	135	3,058.3	44.1 (36.7–51.6)	110	7,660.1	14.4 (11.7–17.0)
Men	135	3,742.5	36.1 (30.0–42.2)	51	6,138.7	8.3 (6.0–10.6)
Age at T0						*
65–69	134	3,487.5	38.4 (31.9–44.9)	46	6,222.6	7.4 (5.3–9.5)
70–74	93	2,105.1	44.2 (35.2–53.2)	60	4,477.6	13.4 (10.0–16.8)
75–79	34	866.7	39.2 (26.0–52.4)	32	2,170.3	14.7 (9.6–19.9)
≥80	9	341.5	26.3 (9.1–43.6)	23	928.3	24.8 (14.7–34.9)

CI, confidence interval; T0, Italian Longitudinal Study on Aging first survey carried out in 1992–1993; T2, Italian Longitudinal Study on Aging third survey 2000–2001. * $p < 0.05$. [a] Incidence rates per 1,000 person-years

(95% CI: 73.6–93.8) for the T0–T1 interval; 11.7 (95% CI: 9.9–13.5) and 39.7 (95% CI: 35.0–44.4) for the overall follow-up period T0–T2 (mean age at T0 71.4 years). Incidence rates of frailty were higher among women than men, although the result of the first follow-up period just failed to reach statistical significance at the 5% *p* level. A trend in the association between frailty incidence rates and age classes was detected, with increasing rates with advancing age ($p = 0.0208$ for T0–T1, $p = 0.0415$ for T0–T2). Pre-frailty incidence rates were significantly higher for women than men for the T0–T1 period, while for T0–T2 the difference was only marginally significant. No significant age trend was detected concerning pre-frailty incidence rates.

Independently from age and sex, the incidence rates of frailty were always considerably higher among participants classified as pre-frail at previous survey than among those who were non-frail at entry to the follow-up period; T0–T1, 1.9 (95% CI: 0.5–3.3) from non-frail versus 14.1 (95% CI: 9.8–18.5) from pre-frail; T0–T2, 6.4 (95% CI: 4.6–8.2) from non-frail versus 18.5 (95% CI: 15.0–21.9) from pre-frail (online suppl. Table 3).

Association with Incident Disability

Among subjects with frailty assessment at T0 who were independent in all ADL at baseline ($n = 1,855$), new cases of disability in at least one ADL were 172 at T1 (9.3%; 12.4% of pre-frail and 20.8% of frail at baseline) and 413 at T2 (22.3%; 27.5% of pre-frail and 56.3% of frail at baseline). The corresponding figures for subjects free from IADL disability at baseline ($n = 1,651$) amounted to 358 new cases at T1 (21.7%; 27.8% of pre-frail, and 44.0% of frail at baseline) and 707 at T2 (42.8%; 48.1% of pre-frail and 68.0% of frail at baseline) (weighted data, not shown).

Table 4 reports the results of the Cox proportional hazard models fitted into data to investigate the association between frailty status at baseline (T0) and incident disability in ADL or IADL observed in the two follow-up periods of 4 and 9 years duration. Data are presented in sex-aggregated form, having verified that the interaction with sex was not statistically significant in any Cox model. In comparison with robust individuals, pre-frail and frail subjects at baseline had a significantly higher risk of incident dis-

Table 4. Association of frailty and pre-frailty at baseline (T0) with incident disability in ADL or IADL at second (T1) and third (T2) ILSA surveys (weighted data)

Frailty status at T0	Incident disability in ≥1 ADL		Incident disability in ≥1 IADL	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
T0–T1				
Model 1*				
Pre-frail	2.08 (1.57–2.75)	<0.0001	1.80 (1.48–2.19)	<0.0001
Frail	4.92 (2.80–8.64)	<0.0001	3.36 (2.12–5.33)	<0.0001
Model 2**				
Pre-frail	1.82 (1.34–2.47)	0.0001	1.65 (1.34–2.05)	<0.0001
Frail	3.58 (1.97–6.52)	<0.0001	2.56 (1.58–4.16)	<0.0001
T0–T2				
Model 1*				
Pre-frail	1.88 (1.57–2.25)	<0.0001	1.46 (1.27–1.68)	<0.0001
Frail	3.18 (2.33–4.34)	<0.0001	2.37 (1.74–3.24)	<0.0001
Model 2**				
Pre-frail	1.79 (1.48–2.17)	<0.0001	1.46 (1.26–1.69)	<0.0001
Frail	2.46 (1.74–3.48)	<0.0001	1.73 (1.16–2.58)	0.0068

HR and 95% CI based on Cox proportional hazard regression models with outcome incident disability in ADL or IADL and non-frail at baseline as reference category. * Adjusted for age and sex. ** Adjusted for age, sex, marital status, living alone, years of schooling, smoking habit, alcohol consumption, comorbidity, cognitive impairment, depressive symptoms, and BMI.

ability in ADL and, to a minor extent, IADL, in both follow-up intervals. The magnitude of the association was stronger for frailty than pre-frailty (risk of incident ADL disability almost twice as high in the frail group), and it was more evident in the short-term than in the longer follow-up period and was confirmed, although slightly weakened, even after adjustment for potential confounders. As shown in the fully adjusted models of Table 4, the risk of becoming dependent in one or more ADL in the 4-year period T0–T1 was more than three times higher (HR 3.58, 95% CI: 1.97–6.52) among frail than non-frail subjects at baseline, and the risk of incident IADL disability in the same group was more than double (HR 2.56, 95% CI: 1.58–4.16). Over the same follow-up period T0–T1, the risk of incident dependence in ADL and IADL was increased by about 80% and 60%, respectively, among pre-frail as compared to the non-frail counterpart.

Discussion/Conclusion

To the best of our knowledge, this is the first comprehensive longitudinal analysis of the frequency of frailty status and of its impact on incident disability, conducted on a nationally representative population-based sample of older Italians. Its main findings can be summarized as follows. (1) The overall prevalence at baseline (mean age 71.6) was 4.0% for frailty and 44.6% for pre-frailty; it was greater for women – frailty prevalence about twofold that of men – increased with age and was more frequent in subjects in the worst socio-economic and health conditions. (2) The estimated incidence rates per 1,000 person-years amounted to 7.3 new cases of frailty and 83.7 of pre-frailty for the T0–T1 interval (mean follow-up duration 4 years) and to 11.7 and 39.7, respectively, for the overall follow-up period T0–T2 (mean duration 9 years). Rates were higher for women, with an increasing trend with advancing age evident only for frailty. (3) Even after adjustment for socio-economic, clinical, and subclinical conditions, frailty and, to a lesser degree, pre-frailty were powerful and independent predictors of disability, accounting for a remarkably higher risk of developing dependence in ADL (HR 3.58 frailty; HR 1.82 pre-frailty) or IADL (HR 2.56 frailty; HR 1.65 pre-frailty) over a 4-year period.

Our prevalence findings were slightly lower than those reported by analogous research conducted in Italy [10], including a previous study on a subsample of the ILSA cohort [25]; while were very similar to those registered in a secondary analysis of the Toledo Study of Healthy Ageing [26]. In this respect, it is important to remark the great variability of

published evidence on frailty prevalence, usually attributable to methodological discrepancies in the sample characteristics or in the frailty definition [13, 14]. This was highlighted in a review of six frailty studies very similar to the present work (Fried definition, population-based sample, aged ≥65 years), which reported prevalence results ranging from 4.9% to 27.3% for frailty and from 34.6% to 50.9% for pre-frailty [27]. However, our findings could be somewhat underestimated, being based on a secondary analysis of frailty data, originally collected for other purposes.

This work represents one of the few longitudinal studies of frailty and one of the very few calculating incidence in person-time rates [28, 29]. As stated in a recent meta-analysis of global frailty incidence, actual data on person-years were unavailable in more than 90% of the 46 reviewed studies [16]. All studies retrieved through a prior review of scientific literature were based on incidence proportions, with reported results extremely heterogeneous (9–13.0%), depending on very different follow-up durations, sample characteristics, and adopted definitions [15]. The few measurements of frailty incidence in person-time rates available from the scientific literature appear higher than ours – i.e., 60.6 per 1,000 person-years, age ≥60 years [28]; 6.8 per 100 person-years, age ≥75 years [29]; frailty 40.0, pre-frailty 150.6 per 1,000 person-years, pooled sample ≥60 years [16] – but were based on studies very different and hardly comparable. Thus, the possibility of validly contrasting our incidence results with previously published findings is quite limited. Nevertheless, the higher incidence of frailty found among subjects previously assessed as pre-frail, in contrast with those initially non-frail, is consistent with most previous observations [16, 19, 28] and highlights the relevance of pre-frailty as a valid target for frailty prevention.

The comparison of incidence rates obtained in the two follow-up segments under investigation shows some differences, at equal mean age of participants at entry (71.4 years) but almost double follow-up length (mean follow-up duration 4 and 9 years). The incidence rates of pre-frailty in the longer interval T0–T2 are about half those observed in the shorter interval T0–T1, while a slight increase in the incidence rates of frailty is observed in the overall follow-up period T0–T2. This suggests that, given the complex fluctuating nature of frailty, linked to a progressive deterioration of physiological integrity in response to repeated stressors [30], the most effective follow-up length for monitoring frailty, and especially pre-frailty, should be at the short/medium term, thus avoiding the selective survival or incidence bias [31] that occurs when subjects with the worst prognosis are also the ones with the highest risk of developing the condition.

Consistently with preexisting evidences, our findings confirmed that occurrence and onset of frailty status were overall more elevated among women than men and increased with advancing age [19, 32–34]. They also confirmed that subjects in the worst health and socio-economic conditions were those with the higher probability of being frail or pre-frail [35, 36]. Further longitudinal investigations, focused on factors related to onset of, and transitions in, frailty status, will be essential to disentangle the temporal ordering of risk and protective factors for frailty. Moreover, in consideration of our finding that slowness was the frailty component that most contributed to frailty or pre-frailty prevalence in all assessments and for both sexes, and strengthened by a recent research showing that some components, including slowness, were present in individuals developing frailty already 6 years prior to the onset [37], a special focus of future research should also be reserved to further longitudinal investigations of the predictive role of single-frailty components.

Applying our prevalence and incidence results to the Italian population aged ≥65 years, according to the 2020 census data, the number of older individuals in frailty conditions should currently exceed the 500,000 cases of frailty and 6,000,000 of pre-frailty; more than half of them should be women. At least 100,000 new cases of frailty and about 1,200,000 of pre-frailty should be expected annually in this fraction of the Italian population. These rough projections are likely to increase over the next decades due to the estimated progressive growth of the older population segment despite the COVID-19 pandemic outburst. Indeed, the current pandemic is severely affecting the routine prevention, care, and control for chronic diseases [38]; therefore, the incidence of frailty is likely to further increase as a collateral damage of COVID-19.

The urgent and growing need for a concerted public health action addressed to frailty was stressed by our findings, not modified by possible confounders, of a significant increased risk of incident disability and dependence in daily activities for frail/pre-frail subjects as compared to non-frail ones. Our findings were comparable to those of prior studies [39, 40] that, consistently with our observation, also reported that the association between frailty and incident disability was stronger at follow-up times under 5 years of observation [40].

The main limitations of the present study are due to the study attrition, with non-participants older and generally in worse health conditions than participants included in the analyses, and to the retrospective approach used for frailty assessment, based on data originally col-

lected with different objectives. This a posteriori use of data might have led to a moderate misclassification of frailty and to a potential underestimate of our results, due to the attrition and loss to follow-up of individuals in worst health and socio-economic conditions, who also represent those at higher probability of being frail. The major strengths of our study are its longitudinal design; the population-based setting; the large size of the sample; the adoption of a weighting based approach to generalize results to the Italian population; and the availability of a comprehensive set of sociodemographic characteristics, clinical, and subclinical conditions, assessed through reliable standardized criteria, to be examined as potential confounders.

In conclusion, as part of a comprehensive longitudinal study of the frequency of frailty status and of its impact on incident disability, carried out on a nationally representative population-based cohort of older Italians, our results confirmed that frailty is a common condition among subjects aged ≥65 years, is deeply related to female sex and advancing age, and is a strong and independent predictor of incident disability, accounting for an increased risk of developing disability about three times higher for frail than non-frail subjects and almost twice for pre-frail ones. According to our first estimate of incidence rates, at least 100,000 new cases of frailty and 1,200,000 of pre-frailty should be expected annually in this fraction of the Italian population over the next decades. Further longitudinal research to investigate the multifaceted and complex determinants of frailty progression, and especially of its remission, will be crucial to orient targeted preventive measures and calibrate an effective public health response.

Appendix

The Italian Longitudinal Study on Aging (ILSA) working group: E. Scafato, G. Farchi, L. Galluzzo, C. Gandin, Istituto Superiore di Sanità, Rome; A. Capurso, F. Panza, V. Solfrizzi, V. Lepore, P. Livrea, University of Bari; L. Motta, G. Carnazzo, M. Motta, P. Bentivegna, University of Catania; S. Bonaiuto, G. Cruciani, D. Postacchini, Italian National Research Centre on Aging (INRCA), Fermo; D. Inzitari, L. Amaducci, University of Florence; A. Di Carlo, M. Baldereschi, Institute of Neuroscience, Italian National Research Council of Italy (CNR), Florence; C. Gandolfo, M. Conti, University of Genoa; N. Canal, M. Franceschi, San Raffaele Institute, Milan; G. Scarlato, L. Candelise, E. Scapini, University of Milan; F. Rengo, P. Abete, F. Cacciatore, University of Naples; G. Enzi, L. Battistin, G. Sergi, G. Crepaldi, University of Padua; S. Maggi, N. Minicuci, M. Noale, Institute of Neuroscience, Italian National Research Council (CNR), Aging Section, Padua; F. Grigoletto, E. Perissinotto, Institute of Hygiene, University of Padua; P. Carbonin, Università Cattolica del Sacro Cuore, Rome.

Statement of Ethics

The ILSA study was conducted according to the guidelines laid down in the World Medical Association Declaration of Helsinki. The study protocol and all procedures involving human subjects were reviewed and approved by the Bioethics Committees of the participating centers, which are listed above in the ILSA working group (Maggi S, Zucchetto M, Grigoletto F, Baldereschi M, Candelise L, Scarpini E, Scarlato G, Amaducci L. The Italian Longitudinal Study on Aging (ILSA): design and methods. *Aging (Milano)*; 1994 Dec;6(6):464–73). Written informed consent was obtained from all individual participants before starting the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Lucia Galluzzo conceived the study, had full access to all data, and takes responsibility for the accuracy and integrity of the data analysis. Marianna Noale, Stefania Maggi, and Graziano Onder contributed to the study conception and design and to the interpretation of results. The acquisition and analysis of data were performed by Lucia Galluzzo, Marianna Noale, Alessandro Feraldi, and Marzia Baldereschi e Antonio Di Carlo. The first draft of the manuscript was written by Lucia Galluzzo e Marianna Noale, and all the authors provided critical revision of the manuscript for important intellectual contents. The final version of the manuscript was read and approved by all the authors. The corresponding author (Lucia Galluzzo) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data Availability Statement

The complete dataset that support the findings of this study is not publicly available due to the original agreements regulating ILSA conduction and data management. Any further request of data not included in this article and/or in its online supplementary material can be directed to the corresponding author.

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